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ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/577,489	WOOD ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36,39,40,42,43,51-60 and 64-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36,39,40,42,43,51-60 and 64-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-36, 39-40, 42-43, 51-60, and 64-72 are pending. Applicants previously cancelled claims 1-27, 37-38, 41, 44-50, and 61-63. Receipt and consideration of Applicants' remarks/arguments and Dr. Bosch's 1.132 declaration submitted on August 30, 2010 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Priority

The effective filing date of the instant application is February 24, 1995.

Election/Restrictions

The species elections for asthma as the respiratory disease in a mammal and corticosteroids as the elected therapeutic agent are maintained and remain in effect.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Consideration of Dr. Bosch's 1.132 Declaration

Dr. Bosch's declaration presents data in Table 1 concerning the composition of four different beclomethasone dipropionate (BDP) formulations comprising polyvinyl alcohol (PVAL

as a surface stabilizer and labeled as: (a) Micro I (a suspension comprising micronized BDP and 2.5% PVAL and having a test volume of 1.85 ml), (b) Nano II (a dispersion comprising nanoparticulate BDP and 2.5% PVAL and having a test volume of 1.85 ml), (c) Nano III (a dispersion comprising nanoparticulate BDP and 0.1 % PVAL and having a test volume of 1.85 ml), and (c) Nano IV (a dispersion comprising nanoparticulate BDP and 0.1 % PVAL and having a test volume of 5.85 ml). Table 2 contains data concerning the amount of BDP fraction remaining in the nebulizer and the BDP fraction reaching the impactor. The data in Table 2 indicates that the amount of BDP fraction remaining in the nebulizer was greatest for Micro I and least for Nano IV, whereas the Nano IV formulation had the greatest fraction of BDP reaching the impactor (i.e. ~35%) and the Micro I formulation had the lowest fraction of BPD reaching the impactor (i.e. ~8%).

Dr. Bosch's data is noted, but is not found persuasive or particularly relevant, because the closest prior art reference is Liversidge, which discloses nanoparticulate crystalline formulations having a surface stabilizer adsorbed to the surface of crystalline active agent. Thus, a comparison with Liversidge would be needed. Furthermore, it is noted that Applicants' claims are not limited to formulations wherein the surface stabilizer is polyvinyl alcohol or wherein the surface stabilizer is present in amounts of 2.5% w/w or 0.1 % w/w.[1] Another deficiency in Dr. Bosch's data is that the particle size of the nanoparticulate BDP formulations is not disclosed, such that it would be impossible to know what effect particle size had on the observed results. Similarly the size of the micronized BPD suspension is not disclosed either. It is also unclear whether the differences observed between the Nano III and Nano IV formulations was only due

to the test volume used or whether these formulations had different effective average particle sizes that might also have affected the observed results.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-36, 39-40, 51-60, and 64-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Pavord, I. et al.

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[1] Dr. Bosch's data in Table 1 does not include any units of measurement for the concentration of surface stabilizer,

("Pharmacokinetic optimisation of inhaled steroid therapy in asthma," *Clin. Pharmacokinet.*, 1993 Aug., *25(2)*, abstract only), "Glaxo History" (accessed on October 24, 2008 at www/gsk/com/about/history-noflash.htm) ("Glaxo History") (of record), and the Merck Index, 10th Edition (Merck & Co., Inc.: Rahway, NJ, 1983, entry 1018 on page 144) ("MERCK"), as evidenced by Radhakrishnan (U.S. Patent No. 5,049,389) (of record) and Palmer (U.S. Patent No. 5,208,226).

Applicant Claims

Applicants claim a method treating a respiratory illness in a mammal comprising the steps of (a) providing an aerosol composition comprising aqueous droplets having a particle size of less than 10 microns in diameter, wherein the droplets comprise (i) water, (ii) crystalline particles of beclomethasone having an effective average particle size of less than 1,000 nm (i.e. at least 90% of the particles have a weight average particle size of less than about 1,000 nm, as defined on pg. 16, lines 24-27 of Applicants' specification), (iii) at least one surface modifier adsorbed on the surface of the crystalline beclomethasone particles, and (b) administering the aerosol composition to the lungs of a mammal, wherein the respiratory disease is selected from the group consisting of ***asthma***, emphysema, respiratory distress syndrome, chronic bronchitis, and cystic fibrosis.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Liversidge teaches that dispersible particles consisting essentially **of crystalline poorly soluble drug substance having a surface modifier adsorbed on the surface thereof exhibit**

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but is assumed that the units of measurement were w/w %.

unexpectedly higher bioavailability (title; abstract; col. 1, lines 5-10; col. 2, lines 34-37; and col. 3, lines 3-9). The **effective average particle size of the invented particles is less than about 400 nm** (abstract; col. 2, lines 38-43; col. 5, lines 25-40; claims 1-5). The phrase "**effective average particle size of less than about 400 nm" is defined to mean that at least 90% of the particles have a weight average particle size of less than about 400 nm** (col. 5, lines 25-28). **Preferably, at least 95% and more preferably, at least 99% of the particles have a particles size less than the effective average, such as 400 nm** (col. 5, lines 33-37). In some embodiments, the effective average particle size is less than about 100 nm (col. 5, lines 30-34). Suitable crystalline poorly soluble drugs include **anti-inflammatory agents and *corticosteroids*, and in preferred embodiments the drug substance is a steroid** (col. 3, lines 53-64; col. 4, lines 25-27; and claims 4-5). The drug substances are commercially available or can be prepared by techniques known in the art (col. 4, lines 13-14). Suitable surface modifiers are disclosed from column 4, line 34 through col. 5, line 12 (e.g. sodium lauryl sulfate, lecithin, Pluronic F-68 [i.e. a polymer], etc.). The surface modifiers taught by Liversidge as being suitable are essentially ones recited in Applicants' laundry list in claim 32, for example. **Suitable amounts of surface modifier are taught to be about 0.1-10 mg per square meter surface area of the drug substance (i.e. 0.1-90% w/w, preferably 20-60% w/w, based on the total weight of the dry particle)** (col. 7, lines 10-20).

Liversidge teaches **that the nanoparticles of crystalline drug substance may be obtained by conventional milling techniques, such as air jet and fragmentation milling** (col. 5, lines 50-61). Liversidge provides the necessary guidance to obtain nanocrystalline drug

particles (see col. 5, line 41 through col. 7, line 29; claims 16-20). Liversidge teaches that the compositions may be delivered to mammals (e.g. claim 15).

Merck teaches that **both beclomethasone and its diester- beclomethasone dipropionate- are suitable for the treatment of asthma** (entry 1018 on page 144).

Glaxo history teaches that in 1972 a commercial product comprising the inhaled beclomethasone dipropionate steroid was launched by Glaxo as BECOTIDE® for the treatment of asthma. **BECOTIDE® is an aqueous suspension of beclomethasone dipropionate that is conventionally administered by nebulization** (i.e. it is atomized from a nebulizer) to treat bronchial asthma, which was commercially available at the time of the instant invention, as evidenced by Radhakrishnan (col. 5, lines 43-51). Radhakrishnan's teachings also evidence that beclomethasone dipropionate is **a poorly water-soluble active agent** (col. 4, lines 22-23).

Pavord teaches that that **the recognition that asthma has a large inflammatory component has led to the use of steroids in its treatment** and **the two most widely used steroidal agents to treat asthma are beclomethasone dipropionate** and budesonide (abstract).

Palmer evidences that **beclomethasone dipropionate is an anti-inflammatory corticosteroid** (col. 1, lines 32-34).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Liversidge lacks the teaching of specific corticosteroids. This deficiency is cured by the teachings of Pavord, Merck, and Glaxo History, as evidenced by Radhakrishnan and Palmer.

Finding of Prima Facie Obviousness Rationale and Motivation

(MPEP §2142-2143)

It would have been prima facie obvious to modify the teachings of Liversidge to utilize beclomethasone as a corticosteroid (Palmer), anti-inflammatory (Palmer), or steroid (Palmer, Pavord, and Glaxo) selected to prepare nanoparticulate dispersions, because Liversidge explicitly indicates that suitable active agents include poorly water soluble anti-inflammatory agents, corticosteroids, and steroids and Pavord establishes that at the time of Applicants' claimed invention beclomethasone was one of the two most widely used anti-inflammatory steroids in the treatment of asthma. Furthermore, beclomethasone satisfies the requirement in Liversidge that the selected active agent is poorly water-soluble (Radhakrishnan). Thus, Liversidge and Pavord provide ample motivation for the ordinary skilled artisan to select beclomethasone as an active agent used to make nanoparticulate pharmaceutical suspensions commensurate in scope with Liversidge's teachings. Regarding the preparation of aqueous suspensions of beclomethasone an ordinary skilled artisan would have been motivated to obtain aqueous suspensions of nanoparticulate crystalline beclomethasone per Liversidge's teachings, because at the time of the instant invention beclomethasone was commercially available as an aqueous suspension marketed under the BECOTIDE® trademark and sold by Glaxo ("Glaxo History"). The BECOTIDE® product was known to contain beclomethasone dipropionate at a concentration of 50 micrograms/ml, as evidenced by Radhakrishnan. An ordinary skilled artisan would have been further motivated to use Liversidge's technology to obtain crystalline nanoparticulate beclomethasone aqueous suspensions, because said suspensions would be reasonably expected to exhibit greater local bio-availability of the beclomethasone (Liversidge) and would reasonably be expected to reach a patient's alveoli upon inhalation of an aqueous suspension of

nanoparticulate crystalline beclomethasone, due to the small size of the suspended crystalline beclomethasone.

Regarding particle size of the crystalline beclomethasone and the amount of surfactant, the combined prior art teaches overlapping ranges. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Regarding the amount of beclomethasone suspended in the formulation, the commercially available BECOTIDE® product contained a concentration of beclomethasone dipropionate of 0.05% w/w, which reads on an amount of beclomethasone of about 0.1% w/w as recited in dependent claim 39. Concerning the amount of beclomethasone recited in Applicants' dependent claim 40, it is the Examiner's position that the ordinary skilled artisan would have been motivated to modify (i.e. increase or decrease) the concentration of beclomethasone based upon a patient's response to a particular dosage of beclomethasone therapy. Thus, it would have been prima facie obvious to utilize different dosages, and the ordinary skilled artisan would have arrived at dosage of from about 5% to about 30% w/w as is recited in Applicants' claim 40. Absent some demonstration of unexpected results from the claimed dosage range, the optimization of the amount of beclomethasone would have been obvious at the time of applicant's invention.

Regarding the recitation of beclomethasone and not beclomethasone dipropionate, the ordinary skilled artisan would consider the beclomethasone to be interchangeable with beclomethasone dipropionate, because both compounds are known to be suitable for the treatment of asthma, are poorly water-soluble, and are anti-inflammatory corticosteroids. Applicants' tabulated specification data is noted, and is does not demonstrate any unexpected or

surprising results. Dr. Bosch's declaration data is noted, but is found unpersuasive for the reasons set forth above. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments with respect to claims 28-36, 39-40, 51-60, and 64-72 have been considered but are moot in view of the new ground(s) of rejection. Because the Liversidge and Radhakrishnan references form part of the instant rejection Applicant's arguments regarding these references are addressed below.

Applicants traversal arguments considered relevant to the instant are: (1) the Liversidge reference allegedly does not recite any preferences of any drug classes; (2) there is allegedly no reason based on the teachings of Liversidge to select a steroid; (3) allegedly only improper hindsight and ignores would motivate the ordinary skilled artisan to select beclomethasone; (4) Applicants' argument (3) is supported by the holding in *Takeda Chemical Industries v. Alphapharm Pty*., 492 F.3d 1350, 1357, 83 USPQ2d 1169, 1170 (Fed. Cir. 2007) that there was a lack of motivation in the prior art discussed in *Takeda*; (5) the rejection allegedly relies on an improper "obvious-to-try" rational, because allegedly it fails to provide the ordinary skilled artisan with a reasonable expectation of success; and (6) Applicants have demonstrated unexpected results with Dr. Bosch's declaration data.

The Examiner respectfully disagrees with Applicants' traversal arguments. Regarding (1)-(2), Applicants' arguments are factually incorrect. Applicants' citation to Liversidge's

teachings at column 4, lines 15-27 contradicts their statement that Liversidge does not identify any preferred classes of compounds, because the cited passage from Liversidge explicitly identifies steroids and antivirals as being preferred classes of drugs. Thus, these arguments are unpersuasive.

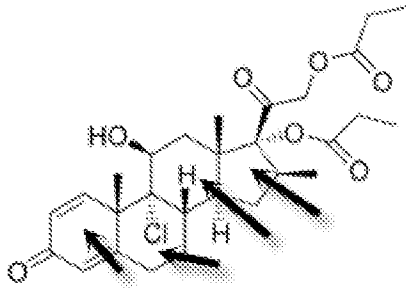
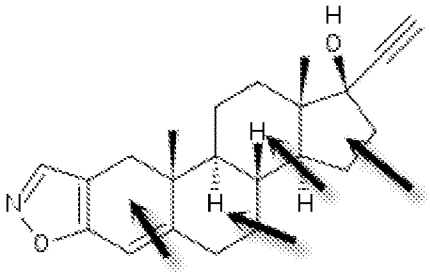
Regarding (3), in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The motivation to select a poorly water-soluble crystalline drug being a steroid is not obtained from improper hindsight, but rather from the teachings of Liversidge (col. 3, lines 53-64; col. 4, lines 25-27; and claims 4-5). It is also noted that Liversidge explicitly identifies corticosteroids and anti-inflammatories as other classes of suitable therapeutics (col. 3, lines 55 and 64 and claim 4). Corticosteroids are a sub-genus of steroids and are known to exhibit anti-inflammatory properties (Palmer), and beclomethasone is a known anti-inflammatory corticosteroid. Furthermore, at the time of Applicants' claimed invention, beclomethasone was one of the two most widely used steroids in the treatment of asthma. Another criterion indicated by Liversidge for a drug in addition to being poorly water-soluble is that it is commercially available or can be readily prepared by methods known in the art. Beclomethasone has commercially since at least 1972 and at the time of Applicants' invention it was available as an aqueous suspension sold under the BECOTIDE®

trademark. Thus, it would have been prima facie obvious to select beclomethasone as a drug prepared into nanoparticulate composition per the teachings of Liversidge, because it meets Liversidge's criteria for a suitable drug (i.e. poorly water-soluble, a steroid, a corticosteroid, an anti-inflammatory, and is commercially available) and was the one of the two most widely used steroids in the treatment of asthma at the time of Applicants' claimed invention.

Applicants' reliance on *Takeda* is misplaced, because the facts of *Takeda* are not analogous to the facts of the instant application or the instant rejection. In *Takeda* the Federal Circuit considered whether it would have been obvious to select compound b from one of hundreds of millions of prior art-disclosed compounds indicated as exhibiting anti-diabetic properties, especially given that compound b had been described as exhibiting the undesirable properties of causing "considerable increases in body weight and brown fat weight." Applicants' citation from the *Takeda* decision cherry picks portions of the cited quotation to support their argument. The omitted part of the cited quotation from *Takeda*, when taken together with what Applicants' cite, demonstrates that the fact pattern in *Takeda* is non-analogous to the instant application, because in *Takeda* the prior art taught away from the selection of compound b and for this reason lacked motivation, whereas the instant rejection relies on a combination of prior art that does not teach away from the selection of beclomethasone and provides ample motivation to select beclomethasone. Thus, Applicants' reliance on *Takeda* to support argument (3) is unpersuasive. The rejection is maintained.

Argument (5) is based on the assertion that the number of possible steroids is so vast that the ordinary skilled artisan would allegedly have no reasonable expectation of success even if it were obvious-to-try each known steroid in Liversidge's method. The Examiner respectfully

disagrees with Applicants' conclusion. There is a reasonable expectation of success, because Liversidge provide several parameters to guide the selection of an appropriate drug. First, Liversidge requires that the selected drug is poorly water-soluble and then limits these to drugs belonging to forty six specific drug classes. Of the drug classes identified, Liversidge identifies a preference for steroids and antivirals. As noted above, at the time of the instant invention beclomethasone was the second most widely used steroid in the treatment of asthma and it was commercially available. Thus, beclomethasone would have been an attractive drug candidate for use in Liversidge's method, because it was approved for use in the treatment of asthma; was widely used for this purpose; and it was commercially available. Secondly, Liversidge provides specific guidelines regarding a simple screening method that can be used to find the appropriate surfactant/drug combinations. Thirdly, it is noted that there is substantial structural similarity between steroids in general, beclomethasone, and the specific steroids utilized in Liversidge. For example, beclomethasone and danazol share the same polycyclic core structure as demonstrated by the four arrows in structures depicted below. Therefore, the ordinary skilled artisan would reasonably expect that if nanoparticulate formulations per the teachings of Liversidge may be made using danazol that one could obtain similar nanoparticulate formulations with beclomethasone with a reasonable predictable expectation of

Beclomethasone:	Danazol:
	

success. Finally, an absolute expectation of success is not the required standard for showing a reasonable expectation of success, and for the aforementioned reasons the ordinary skilled artisan would have had a reasonable expectation of success in obtaining nanoparticulate dispersions based on Liversidge's teachings as applied to beclomethasone as the active agent. The rejection is maintained.

Regarding (4), Applicants cite Radhakrishnan at column 16, lines 61-64 and at column 16, line 66 through column 17, line 2 as teaching the liquid aerosol particle size (i.e. droplet particle size) of BECOTIDE®. Applicants are correct that the cited sections of Radhakrishnan describe droplet particle size, but this observation ignores (i) the fact that the instant rejection is based upon a combination of references; and (ii) the teachings of Liversidge, the primary reference of the instant rejection. Thus, argument (4) is an argument made by attacking the references individually without considering the teachings of the combined references.

Regarding (6), Dr. Bosch's declaration data was not found to be persuasive, for the reasons stated above, which are herein incorporated by reference. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Pavord, I. et al. ("Pharmacokinetic optimisation of inhaled steroid therapy in asthma," *Clin. Pharmacokinet.*, 1993 Aug., *25(2)*, abstract only), "Glaxo History" (accessed on October 24, 2008 at

www/gsk/com/about/history-noflash.htm) ("Glaxo History") (of record), and the Merck Index, 10th Edition (Merck & Co., Inc.: Rahway, NJ, 1983, entry 1018 on page 144) ("MERCK"), as evidenced by Radhakrishnan (U.S. Patent No. 5,049,389) (of record) and Palmer (U.S. Patent No. 5,208,226) as applied to claims 28-36, 39-40, 51-60, and 64-72 above, and further in view of Spear et al. (U.S. Patent No. 5,525,623).

Applicant Claims

Applicants claim a method treating a respiratory illness in a mammal as described above, wherein the nebulizing step is done using a jet nebulizer (claim 42) or an ultrasonic nebulizer (claim 43).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Liversidge, Pavord, Glaxo History, Merck, Radhakrishnan, and Palmer are set forth above.

Spear teaches that **jet nebulizers and ultrasonic nebulizers are conventional means of creating aerosols for use as asthma medication** (col. 13, lines 34-40).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Liversidge lacks the teaching of a jet nebulizer or an ultrasonic nebulizer. These deficiencies are cured by the teachings of Spear.

Finding of Prima Facie Obviousness Rationale and Motivation

(MPEP §2142-2143)

It would have been prima facie obvious at the time of the instant invention to nebulize an aqueous solution comprising beclomethasone dipropionate (BDP) using either an ultrasonic nebulizer or a jet nebulizer, because both nebulizers were conventionally used to administer pharmaceutical aqueous formulations. An ordinary skilled artisan would have been motivated and would have had a reasonable expectation of nebulizing an aqueous pharmaceutical formulation, such as that resulting from the teachings of Liversidge and Radhakrishnan, with a jet nebulizer or an ultrasonic nebulizer, because said nebulizers were conventionally known to be suitable for the inhalation administration of aqueous pharmaceutical formulations and were conventionally used for this purpose (Spear). The use of a device in the matter in which said device was intended to be used is prima facie obvious. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments with respect to claims 42-43 have been considered but are moot in view of the new ground(s) of rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-33, 39-40, 51-60, 66, 69, and 72 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9-11, and 13-14 of copending Application No. 10/035,324 (copending '324) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claim 1 of copending '324 claims a sterile, stable, nanoparticulate dispersion comprising (i) a liquid dispersion medium, (ii) nanoparticulate beclomethasone particles having an effective particle size of less than 150 nm, (iii) tyloxapol as a surface stabilizer adsorbed onto the surface of the beclomethasone nanoparticles, and (iv) optionally at least one secondary surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone.

The primary differences between the claim 28 of the instant application and claim 1 of copending '324 are that claim 1 of copending '324 does not (1) recite a method of treating a respiratory illness, (2) does not specify that the nanoparticulate beclomethasone is crystalline, (3)

does not specify that the liquid dispersion medium is water, and (4) does not recite the delivery of the dispersion as droplets. Regarding (1) and (3)-(4), these deficiencies are cured by the teachings of Liversidge and Radhakrishnan, as set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is known to use water as a suspension/dispersion medium; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Regarding deficiency (2), dependent claim 11 of copending '324 evidences that it was contemplated for the beclomethasone nanoparticles to be crystalline. Thus, the formulation of the claimed nanoparticulate dispersions of copending '324 is an obvious modification of this formulation. Regarding particle size, the particle size recited in the claims of copending '324 overlap with the particle size ranges recited in the instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. It is noted that tyloxapol is one of the specific surface stabilizers recited in dependent claim 32 of the instant application. Regarding the additional possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 9 of copending '324. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-33, 39-40, 51-60, 66, 69, and 72 *prima facie* obvious over claims 1-7, 9-11, and 13-14 of copending Application No. 10/035,324 (copending '324) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicants did not traverse the instant rejection. The rejection is maintained.

Claims 28-33, 53-60, 66, 69, and 72 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 60-61, 64-65, 69-70, and 72-76 of copending Application No. 10/768,194 (copending '194) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claim 60 of copending '194 claims a method of treating a subject in need of either symptomatic or prophylactic treatment comprising administering to said subject an effect amount of sterile particulate fluticasone composition comprising (i) particles of fluticasone (i.e. an anti-inflammatory steroid) having an effective average particle size of less than 150 nm and (ii) at least one surface stabilizer.

The primary differences between claim 60 of copending '194 and claim 1 of the instant application are that claim 60 of copending '194 does not (1) specify that the disease being treated is a respiratory disease (e.g. asthma); (2) does not recite particles of beclomethasone; (3) does not specify that the particulate composition is an aqueous dispersion; and (4) does not specify that the particulate active agent is crystalline. Deficiencies (2)-(3) are cured in part by the teachings of Liversidge and Radhakrishnan set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is known to use water as a suspension/dispersion medium; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer.

Liversidge also establishes that anti-inflammatory steroids are suitable for incorporation into nanoparticulate dispersions (col. 3, lines 53-55 and 64; col. 4, lines 25-26; Example 1 through Example 14: col. 8, line 35 through col. 13, line 53). Regarding deficiencies (1) and (4), dependent claims 64-65 and 69 evidence that it is obvious to modify the claimed method of treatment of copending '194 to treat asthma and to utilize crystalline particulate fluticasone in the administered composition, respectively. Regarding particle size, the particle size recited in the claims of copending '194 overlap with the particle size ranges recited in the instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. It is noted that tyloxapol is one of the specific surface stabilizers recited in dependent claim 32 of the instant application. Regarding the additional possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 76 of copending '194. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-33, 53-60, 66, 69, and 72 *prima facie* obvious over claims 60-61, 64-65, 69-70, and 72-76 of copending Application No. 10/768,194 (copending '194) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicants did not traverse the instant rejection. The rejection is maintained.

Claims 28-36 and 51-60 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claims a nanoparticulate composition comprising (i) beclomethasone dipropionate particles having an average particle size of less than about 1,000 nm and (ii) at least one surface modifier.

The primary differences between the claim 28 of the instant application and claim 1 of copending '092 are that claim 1 of copending '092 does not (1) recite a method of treating a respiratory illness, (2) does not specify that the nanoparticulate beclomethasone is crystalline, (3) does not recite an aqueous dispersion medium, and (4) does not recite the delivery of the dispersion as droplets. Regarding (1)-(2) and (4), these deficiencies are cured by the teachings of Liversidge and Radhakrishnan, as set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is desirable to use nanoparticulate crystalline solids in a liquid dispersion medium to obtain formulations exhibiting unexpectedly improved bio-availability; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Regarding deficiency (2), dependent claim 11 of copending '092 evidences that it was contemplated for the beclomethasone nanoparticles to be formulated as an aqueous dispersion. Thus, the formulation of the claimed nanoparticulate beclomethasone dipropionate of copending '092 is an obvious modification of this formulation. Regarding particle size, the particle size range recited in the claims of copending '092 overlaps with the particle size ranges recited in the

instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Regarding the possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 17 of copending '092. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-36 and 51-60 *prima facie* obvious over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicants did not traverse the instant rejection. The rejection is maintained.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Lacy, C. et al. (Drug Information Handbook, Lexi-Comp, Inc.: Cleveland, 1993, pp 95-96) is relevant because it identifies other commercially available pharmaceutical formulations of beclomethasone known at the time of Applicants' invention. Hansbrough, J. R. and Shapiro, S. D. ("Pulmonary Diseases" in *The Washington Manual: Manual of Medical Therapeutics, 27th edition*, Glaxo, St. Louis, Missouri: **1992**, pp 196 and 199) is relevant because it demonstrate that

beclomethasone was one of a few inhaled corticosteroids routinely indicated for the treatment of asthma at the time of Applicants' claimed invention.

Claims 28-36, 39-40, 42-43, 51-60, and 64-72 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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